



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/699,030	10/26/2000	Shiy Kumar	030516.0029CON1	3324

30542 7590 10/28/2004

FOLEY & LARDNER
P.O. BOX 80278
SAN DIEGO, CA 92138-0278

EXAMINER

FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
----------	--------------

1637

DATE MAILED: 10/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/699,030	KUMAR ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 October 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13 and 18-45 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 5-8 and 10-13 is/are allowed.
- 6) ☒ Claim(s) 1-4,9 and 18-45 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status

1. Claims 1-13 and 18-45 are pending.

Claims 5-8 and 10-13 are allowed.

Claims 1-4, 9 and 18-45 are rejected.

The application has a somewhat unclear provenance for the current amendment. The amendment was filed twice, first with a certificate of mailing date of March 15, 2004 and second with a certificate of mailing date of October 14, 2004. In addition, there is a petition to revive for unintentional abandonment filed October 14, 2004. The petition lacks a definite statement that the previous amendment was not placed in the mail. Consequently, the Patent office has no evidence to support an abandonment, and a resulting need for revival, but must accept the certificate of mailing for the amendment filed March 15, 2004, since a certification by a registered Patent practitioner is accepted under 37 CFR 1.8.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 3, 9 and 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evangelista et al (Anal. Biochem. (1996) 235:89-97).

Evangelista teaches a compound of formula (I) (A-B-C) with a cyanine dye which meets the structural requirements of A, a linker of more than 10 atoms in length as required by B, and attached to the 5 position of dUTP, which has a triphosphate attached (page 91, figure 1). It should be noted, that because the attachment is at the 5 position, dUTP and dTTP yield identical structures.

Evangelista does not teach a structure where this compound is a dideoxynucleotide.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to modify the labeled deoxynucleotide of Evangelista into a dideoxynucleotide since Evangelista notes "Fluor-labeled deoxynucleotide triphosphates (dNTPs) or dideoxynucleoside triphosphates (ddNTPs) are employed in nonradioactive DNA sequencing techniques such as those developed by Prober et al (ref omitted) and Ansorge et al (ref omitted) as well as for incorporation into hybridization probes (ref omitted). Fluorescent ddNTPs have also been used as terminal deoxynucleotidyl transferase substrates to label single (ref omitted) and double

Art Unit: 1637

stranded DNA (ref omitted) (page 89, column 1, last sentence to page 89, column 2)".

An ordinary practitioner would have been motivated to alter the dNTP dyes of Evangelista into ddNTP dyes in order to permit nonradioactive DNA sequencing, hybridization probe or terminal transferase methods to be used as expressly taught by Evangelista. An ordinary practitioner would have had a very high expectation of success since it is routine to make both dNTP and ddNTPs with the same label as discussed by Evangelista on page 89, column 2. It would have been further obvious to utilize the ddNTP resulting from this synthesis in a DNA sequencing method to yield a DNA which comprises the ddNTP.

With regard to claims 22-25, given that there are only four natural ddNTPs, and given Evangelista's express suggestion of ddNTPs, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to make any of the four ddNTPs, including ddA, ddG, ddC and ddT.

5. Claims 1-3, 9, 18-25 and 33-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evangelista et al in view of Tabor et al (U.S. Patent 5,614,365).

Evangelista teaches a compound of formula (I) (A-B-C) with a cyanine dye which meets the structural requirements of A, a linker of more than 10 atoms in length as required by B, and attached to the 5 position of dUTP, which has a triphosphate attached (page 91, figure 1). It should be noted, that because the attachment is at the 5 position, dUTP and dTTP yield identical structures. Evangelista further notes "Our DNA labeling results indicate that the distance provided by the 10-atom spacer arm between the pyrimidine ring and the rather bulky cyanine label is sufficient to allow base pairing

Art Unit: 1637

between the deoxyadenosine and deoxyuridine at the ends of the DNA fragments (page 97, column 1)".

Evangelista does not teach the use of a modified thermostable polymerase nor does Evangelista teach placement of the reagents into a kit.

Tabor teaches the use of modified thermostable polymerases in DNA sequencing reactions (column 5, lines 38-58). Tabor further teaches placement of the reagents into a kit (column 9, lines 57-62).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the fluorescently labeled ddNTPS which are made obvious by Evangelista into a kit with the modified thermostable polymerases of Tabor since Tabor notes "By modification of these enzymes using methods shown below, those in the art can now modify any desired thermophilic DNA polymerase to make it incorporate dideoxynucleotides more efficiently. Such enzymes will be superior to those existing in the present day for DNA sequencing both in automated machines and in manual sequencing, especially in procedures known as cycle sequencing (column 5, lines 46-53)". An ordinary practitioner would have been motivated to form a kit with ddNTPs as made obvious by Evangelista for the improved sensitivity of the dyes (page 96, column 2) as shown by Evangelista and for the use of a superior enzyme as expressly taught by Tabor. An ordinary practitioner would have been motivated to form a kit since with the use of a kit, one need not purchase gram quantities of multiple reagents, each of which is needed in only microgram amounts, when beginning a series

Art Unit: 1637

of experiments. Further, the kit format saves money and resources by dramatically reducing waste. The other advantage provided in a kit is quality control.

6. Claims 3, 4, 9 and 22-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evangelista in view of Haralambidis et al (Nucleic Acids Research (1987) 15(12):4857-4876).

Evangelista teaches a compound of formula (I) (A-B-C) with a cyanine dye which meets the structural requirements of A, a linker of more than 10 atoms in length as required by B, and attached to the 5 position of dUTP, which has a triphosphate attached (page 91, figure 1). It should be noted, that because the attachment is at the 5 position, dUTP and dTTP yield identical structures. Evangelista further notes "Our DNA labeling results indicate that the distance provided by the 10-atom spacer arm between the pyrimidine ring and the rather bulky cyanine label is sufficient to allow base pairing between the deoxyadenosine and deoxyuridine at the ends of the DNA fragments (page 97, column 1)".

Evangelista does not teach the specific linkers of claim 4.

Haralambidis teaches a linker (page 4860, figure 1) which is identical to the fourth claimed linker of claim 4, where the linker links to a nitrogen, as occurs in the structure of Evangelista.

With regard to claim 26, Haralambidis teaches a linker with a triple bond (see page 4860, figure 1).

With regard to claims 27-32, Haralambidis teaches "There is a definite improvement in the ability of the synthetic oligonucleotide to hybridize onto mRNA as

Art Unit: 1637

the distance of the fluorescent moiety from the oligonucleotide backbone increases. Thus, oligonucleotides bearing the short linker arm hybridize considerably less efficiently than the corresponding probes carrying the long linker (see page 4874)."

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the dye labeled compound rendered obvious by Evangelista with the linker of Haralambidis since Haralambidis states "In this paper we have described a method for the synthesis of C-5 substituted deoxyuridine nucleosides, with the substituent carrying a masked primary aliphatic amino group. This method is exceptionally mild and gives the desired compound in high yield (page 4874)". Haralambidis further notes "It was found that oligonucleotides carrying a long (11 atom) linker arm to the fluorescein hybridize more efficiently to mRNA than those carrying a short (4 atom) arm (abstract, page 4857)". An ordinary practitioner would have been motivated to utilize the long linker arm of Haralambidis in the synthesis of the cyanine dye of Evangelista for the expressly stated benefits of mild conditions, high yield and efficient hybridization.

Further, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use longer linker arms since Haralambidis teaches "There is a definite improvement in the ability of the synthetic oligonucleotide to hybridize onto mRNA as the distance of the fluorescent moiety from the oligonucleotide backbone increases. Thus, oligonucleotides bearing the short linker arm hybridize considerably less efficiently than the corresponding probes carrying the long linker (see page 4874)." An ordinary practitioner would have been motivated to make longer arms

Art Unit: 1637

in order to improve the ability of the oligonucleotide to hybridize. With regard to the specific lengths claimed, an ordinary practitioner would have recognized that the results optimizable variables of linker length could be adjusted to maximize the desired results based upon the motivation of Haralambidis. As noted in *In re Aller*, 105 USPQ 233 at 235,

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific times for amplification was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

7. Claims 3, 4, 9 and 22-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evangelista in view of Haralambidis et al (Nucleic Acids Research (1987) 15(12):4857-4876) and further in view of Tabor et al (U.S. Patent 5,614,365).

Evangelista in view of Haralambidis teach the limitations of claims 3, 4, 9 and 22-32 as discussed above, and teach the additional limitations of claimed 33-45 for the reasons discussed above. Evangelista in view of Haralambidis do not teach all of the elements of claim 1.

Tabor teaches the use of modified thermostable polymerases in DNA sequencing reactions (column 5, lines 38-58). Tabor further teaches placement of the reagents into a kit (column 9, lines 57-62).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the fluorescently labeled ddNTPS which are made obvious by Evangelista in view of Haralambidis into a kit with the modified thermostable polymerases of Tabor since Tabor notes "By modification of these enzymes using methods shown below, those in the art can now modify any desired thermophilic DNA polymerase to make it incorporate dideoxynucleotides more efficiently. Such enzymes will be superior to those existing in the present day for DNA sequencing both in automated machines and in manual sequencing, especially in procedures known as cycle sequencing (column 5, lines 46-53)". An ordinary practitioner would have been motivated to form a kit with ddNTPs as made obvious by Evangelista for the improved sensitivity of the dyes (page 96, column 2) as shown by Evangelista and for the use of a superior enzyme as expressly taught by Tabor. An ordinary practitioner would have been motivated to form a kit since with the use of a kit, one need not purchase gram quantities of multiple reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. Further, the kit format saves money and resources by dramatically reducing waste. The other advantage provided in a kit is quality control.

Allowable Subject Matter

8. Claims 5-8 and 10-13 are allowed.
9. The following is a statement of reasons for the indication of allowable subject matter: These claims are drawn to compounds with specific structural formula which are not taught or suggested by the cited prior art such as Evangelista.

Response to Arguments

10. Applicant's arguments filed March 15, 2003 have been fully considered but they are not persuasive.

Applicant argues that the ordinary practitioner would not have known how to make ddG, ddC or ddA from the teaching of Evangelista. This argument is incorrect since Evangelista clearly teaches synthesis of the label with dA, dC and dT, and the ordinary practitioner, provided with the motivation of Evangelista, could easily synthesize dG (see page 91, figure 1).

With regard to the length of the linker, Applicant is referred to the revised rejections and new rejection written above which address this issue.

With regard to the obviousness of Evangelista, these arguments have been addressed and answered in the previous action.

To the extent that Applicant argues unexpected results, there is no evidence of any such results and the claims are not commensurate in scope with any such unexpected results.

Applicant's remaining arguments were already addressed in the previous action and that response is maintained.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Jeffrey Fredman
Primary Examiner

10/21/07